

Application No.: 10/030,803
Filing Date: April 9, 2002
Page No.: 13

REMARKS

Claims 1 through 16, 18 and 19 and new Claims 20 through 24 are pending in the above-referenced application.

Claims 1, 2, 3, 10, 11 and 12 have been amended to remove all reference to non-elected aspects, in particular to remove all references to "Formula (II)" including "Y" and "D." Support for this amendment can be found in the Application-as-filed.

Claims 1, 2, 10, 11 and 19 have also been amended to reflect that the hydrophilic, nonionic polymer advantageously has a lower molecular weight limit of 5000 g/mol. Support for this amendment can be found in the Application-as-filed, for example in Claims 3 and 12 as-filed.

Claims 1, 2, 3, 10, 12 and 19 have further been amended to reflect that the polyethyleneimine (PEI) advantageously further includes a moiety $[A^-]_w$, where A^- is an equivalent of an anion and w is an integer selected to balance the positive charges in the polyethyleneimine(PEI). Support for this amendment can be found in the Application-as-filed, for example on Page 6, lines 1 through 16.

Claims 1, 2, 10, 11 and 19 have been amended to reflect that in advantageous embodiments in which $X = -O(CH_2)_pC(O)-$, p is not 2. Support for this amendment can be found in the Application-as-filed.

Claims 5, 7, 9 and 16, directed to non-elected subject matter, have been canceled without prejudice or disclaimer to the filing of continuing applications thereon.

Claims 4, 17 and 18 have been cancelled without prejudice or disclaimer to the filing of continuing applications thereon.

Application No.: 10/030,803

Filing Date: April 9, 2002

Page No.: 14

Claims 20 through 24 were added to complete the record for examination and highlight advantageous embodiments of the invention.

Claim 20 is directed to advantageous inventive complexes in which the hydrophilic, nonionic, branched polymer residue is a cyclic, star, dendritic, 4-arm, 8-arm or 20-arm polyethylene glycol polymer. As indicated above, support for Claim 20 can be found in the Application-as-filed, for example on Page 5, lines 18 through 14 and Page 18, lines 5 through 16.

Claim 21 is directed to beneficial aspects of such advantageous complexes in which the hydrophilic, nonionic, branched polymer residue is an 8-arm or 20-arm polyethylene glycol polymer. As indicated above, support for Claim 21 can be found in the Application-as-filed, for example on Page 24, lines 18 and 26.

Claim 22 is directed to advantageous inventive complexes comprising (i) linear or branched polyethyleneimine (PEI) and (ii) branched polyethylene glycol that is linked via the group $-OC(O)NH(CH_2)_oNHC(O)-$ and in which o is selected from 1 to 20. Support for Claim 22 can be found in the Application-as-filed, for example on Page 5, lines 18 through 14; Page 18, lines 5 through 16 and Page 24, lines 18 and 26.

Claim 23 has been added to reflect that the moiety A^- is advantageously selected from OH^- , Cl^- and Br^- . Support for Claim 23 can be found in the Application-as-filed, for example on Page 6, lines 1 through 2.

Claim 24 is directed to advantageous surfactants comprising a compound according to Claim 1. Support for Claim 24 can be found in the Application-as-filed, for example on Page 44, lines 7 through 9, as well as Claim 10 of parent international application PCT/EP00/06214.

Application No.: 10/030,803
Filing Date: April 9, 2002
Page No.: 15

Reexamination and reconsideration of this application, withdrawal of all rejections, and formal notification of the allowability of the pending claims are earnestly solicited in light of the remarks which follow.

Election/Restriction

Applicants respectfully submit that a single formula, Formula (I) has been elected, albeit with strong traverse. Accordingly, all reference to Formula (II), including references to "Y" and "D" have been deleted from the pending claims. Furthermore, Claims 5, 7, 9 and 16, directed to non-elected subject matter, have been canceled without prejudice or disclaimer to the filing of continuing applications thereon.

Applicants continue to respectfully submit that no specific "A," "X" or "n" be elected, as generic claims are widely recognized under United States practice. Nevertheless, out of an abundance of caution, Applicants respectfully submit Claim 22 to ensure pendency of the case. Claim 22 is directed to inventive complexes that include (i) a compound having the formula $A(-X-B)_n$ and (ii) polynucleic acid. In the advantageous embodiments of Claim 22, A is branched polyethylene glycol; B is a linear or branched polyethyleneimine; X is $-OC(O)NH(CH_2)_oNHC(O)-$ and o is selected from 1 to 20. As noted above, support for Claim 22 can be found in the Application-as-filed.

Applicants respectfully traverses the withdrawal of Claims 14 and 15, as they are directed to methods associated with elected Formula (I).

Applicants respectfully submit that Claims 1, 2, 3, 6, 8, 10 through 15 and 19 are in condition for examination.

Application No.: 10/030,803
Filing Date: April 9, 2002
Page No.: 16

The Claimed Invention is Patentable
in Light of the Art of Record

Claims 1 through 4, 6, 8 and 18 stand rejected as anticipated by United States Patent 5,204,196 to Yokomichi et al. (US 196). Claims 10 through 13 and 19 stand rejected over US 196 in view of Ogris et al. in Gene Therapy, Vol. 6, Issue 4, April 1999, Pages 595 – 605. (Gene Therapy)

Claims 1 through 4, 6, 8, 10 through 13, 18 and 19 stand rejected as anticipated by WO 9859064. (WO 064). Applicants respectfully submit that United States Published Application 2001/0005717 to Wagner et al (US 717) is an English equivalent of WO 064. Accordingly, remarks below directed to US 717 are intended to distinguish WO 064 as well.

It may be helpful to briefly consider the invention before addressing the merits of the rejection.

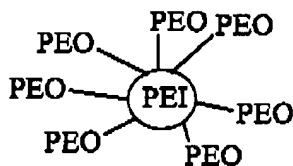
The benefits of nucleic acid gene transfer are known. The use of polyethyleneimine (PEI) as a gene transfer aid is also known. Unfortunately, PEI imparts an increased tendency for aggregation.

In addition to aggregational issues, compounds suitable for gene transfer must also be able to pass through various parts of the body, such as blood vessels and the like. Accordingly, it has heretofore been believed that there is an overriding need for the smallest possible complexes to allow the resulting compound to be transported within the body. Straight-chain complexes were likewise thought to have the greatest mobility within the body, and thus believed to be most advantageous for gene transfer. (The Examiner's attention is kindly directed to the primary reference, US 717, at Paragraphs [0003] and [0012] in conjunction with [0023], evidencing the state of conventional wisdom.)

Application No.: 10/030,803
Filing Date: April 9, 2002
Page No.: 17

Quite unexpectedly, Applicants have found that a combination of non-ionic polymers, such as polyethylene oxide (PEO), and neutralized PEI can be used to improve the tolerability of PEI. In particular, the combination of non-ionic polymer and a neutralizing anion masks the positive charge of the PEI, thus the charge-mediated effects on cell membranes are reduced.

In particularly advantageous embodiments, the inventive compounds include a cationic core made of polyethyleneimine (PEI) and a hydrophilic shell composed of polyethyleneoxide (PEO); obtained by using a 3- to 10- or even 25-fold excess of polyethyleneimine (PEI) with respect to polyethyleneoxide (PEO). In that regard, the Examiners' attention is kindly directed to the Application-as-filed on Page 9, lines 10 through 11 (stating "This intermediate is reacted with a 3- to 10-fold excess of PEI macromolecules..."), as well as Examples 27 to 54. Applicants have further determined, most unexpectedly, that such compounds are particularly useful for transfection with plasmids and si-RNA. In contrast to conventional linear structures, these advantageous core/shell compounds have the structure:



The cited references do not teach or suggest the claimed invention.

US 196 is directed to conductive polymer compositions having high ion conductivity. (Col. 1, lines 24 – 26). US 196 expressly recommends the inclusion of straight-chain poly(ethyleneimine) within its compositions. (Col. 1, lines 57 – 60). US 196 further teaches that the use of poly(ethylene oxide) ("PEO") having a maximum

Application No.: 10/030,803
Filing Date: April 9, 2002
Page No.: 18

degree of polymerization of 100 (i.e. a molecular weight of 4400). (Col. 1, lines 64 – 66). US 196 expressly notes that higher molecular weight PEO is detrimental to ionic conductivity. (Col. 2, lines 1 – 3).

US 196, expressly teaching a maximum PEO molecular weight of 4400, does not teach or suggest such complexes which include hydrophilic, non-ionic polymer with a recited molecular weight of from 5000 to 10 000 000 g/mol in combination with neutralized PEI. In fact, Applicants respectfully submit that to modify US 196 so as to incorporate PEO having the recited elevated molecular weight would render it unfit for its intended purpose.

Nor does US 916, generically referencing PEO, teach or suggest the beneficial cyclic, star, dendritic, 4-arm, 8-arm or 20-arm branched polyethylene glycol of Claims 20 and 21. And US 916 most certainly does not teach or suggest such beneficial branched polyethylene glycols having a molecular weight of from 5000 to 10 000 000 g/mol. As noted above, US 916 clearly teaches away from such elevated molecular weights.

Accordingly, Applicants respectfully submit that US 196 does not teach or suggest the claimed invention.

Gene Therapy does not cure the deficiencies in US 196.

Gene Therapy is broadly directed to DNA/transferrin-polyethyleneimine complexes which have been “PEGylated” to reduce plasma protein binding and erythrocyte aggregation.

Gene Therapy does not teach or suggest complexes which include a non-ionic polymer with the recited molecular weight of from 5000 to 10 000 000 g/mol. And Gene Therapy most certainly does not teach or suggest such advantageous non-ionic polymers in combination with neutralized PEI.

Application No.: 10/030,803

Filing Date: April 9, 2002

Page No.: 19

Nor does Gene Therapy teach or suggest the beneficial cyclic, star, dendritic, 4-arm, 8-arm or 20-arm branched polyethylene glycol of Claims 20 and 21. And Gene Therapy most certainly does not teach or suggest such beneficial branched polyethylene glycols having a molecular weight of from 5000 to 10 000 000 g/mol.

Accordingly, Applicants respectfully submit that Gene Therapy does not teach or suggest the claimed invention.

There would have been no motivation to have combined US 196 and Gene Therapy. US 196 is directed to conductive compositions having high ion conductivity. Gene therapy is directed to DNA complexes having improved binding and aggregation properties. These are altogether different fields of endeavour and problems solved, to say the least.

However, even combined (which Applicants did not do), the claimed invention would not result. In particular, the combination most certainly would not result in complexes including a combination of neutralized polyethleneimine and hydrophilic, non-ionic polymer with a molecular weight of from 5000 to 10 000 000 g/mol. In fact, there would have been no expectation of success for non-ionic polymers having such elevated molecular weights, given the clear teaching away in US 196.

Nor does the combination teach or suggest the beneficial cyclic, star, dendritic, 4-arm, 8-arm or 20-arm branched polyethylene glycol of Claims 20 and 21. And the combination most certainly does not teach or suggest such beneficial branched polyethylene glycols having a molecular weight of from 5000 to 10 000 000 g/mol.

Accordingly, Applicants respectfully submit that US 196 and Gene Therapy do not teach or suggest the claimed invention, considered either alone or in combination.

Application No.: 10/030,803
Filing Date: April 9, 2002
Page No.: 20

US 717 (and WO 064) likewise fails to teach or suggest the claimed invention.

US 717 is directed to PEI-hydrophilic polymer block copolymers. US 717 teaches that the hydrophilic polymer attached to the PEI should be linear, to maintain its mobility. [0023]. US 717 emphasizes the importance of polymer linearity by going on to state that the "beneficial effects" of the polymer is "attributable" to its mobility. [0023]. Furthermore, in contrast to the claimed complexes, US 717 teaches PEGylation using methoxy-succinimidyl-propionate-PEG alone. [0038 in conjunction with 0087; 0090; 0096; 0115; 0118; 0126; 0154; 0156 and 0165]

US 717 thus does not teach or suggest the recited complexes comprising hydrophilic polymer residue linked to PEI via the extensive list of linkers recited in the claims as-amended.

Nor does US 717, directed to linear polymers providing mobility, teach or suggest core/shell complexes which include hydrophilic, non-ionic polymer with a recited molecular weight of up to 10 000 000 g/mol in combination with neutralized PEI.

And US 717, teaching away from highly branched hydrophilic polymers, most certainly does not teach or suggest the recited cyclic, star, dendritic, 4-arm, 8-arm or 20-arm branched polyethylene glycol of Claims 20 and 21. In fact, there would have been no expectation of success for such branched PEGs based on the teachings of US 717.

However, even if one had looked to US 717 (which Applicants did not), the claimed invention would not result. In particular, US 717, recommending linear hydrophilic polymers linked to PEI via a methoxy-succinimidyl-propionate group, would not result in the recited hydrophilic polymer residue linked to PEI via the numerous linkers recited in the claims as-amended.

Application No.: 10/030,803
Filing Date: April 9, 2002
Page No.: 21

Nor would one looking at US 717 (which, again, Applicants did not) produce compounds including the cyclic, star, dendritic, 4-arm, 8-arm or 20-arm branched polyethylene glycol of Claims 20 and 21.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of US 717 (and thus WO 064), considered either alone or in combination with the remaining art of record.

Foreign Priority Documents

The Office Action kindly indicates that a certified copy of the foreign priority document(s) is not in the electronic file wrapper. Applicants' European Representative has requested that the International Bureau forward a certified copy of the foreign priority document to perfect Applicants' claim for priority, as indicated in attached Exhibit I.

CONCLUSION

It is respectfully submitted that Applicants have made a significant and important contribution to the art, which is neither disclosed nor suggested in the art. It is believed that all of pending Claims 1 through 3, 6, 8, 10 through 15 and 19 through 24 are now in condition for immediate allowance. It is requested that the Examiner telephone the undersigned if any questions remain to expedite examination of this application.

It is not believed that extensions of time or fees are required, beyond those which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time and/or fees are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required is hereby authorized to be charged to Deposit Account No. 50-2193.

Application No.: 10/030,803
Filing Date: April 9, 2002
Page No.: 22

Respectfully submitted,

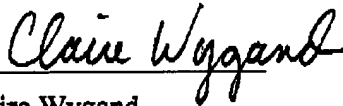


Cathy R. Moore
Reg. No. 45,764

ProPat, L.L.C.
425-C South Sharon Amity Road
Charlotte, NC 28211-2841
Telephone: (704) 365-4881
Fax: (704) 365-4851
Customer No. 38263

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Claire Wygand